Acute Stenting and Concomitant Tirofiban Administration for the Endovascular Treatment of Acute Ischemic Stroke Related to Intracranial Artery Dissections: A Single Center Experience and Systematic Review of the Literature

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Abstract: BACKGROUND Intracranial artery dissection is an uncommon cause of acute ischemic stroke. Although acute stenting of the dissected arterial segment is a therapeutic option, the associated antiplatelet regimen remains a matter of debate. OBJECTIVES To evaluate the efficacy and safety of acute intracranial stenting together with concomitant intravenous administration of tirofiban and to perform a systematic review of the literature. MATERIALS AND METHODS A single-center, retrospective study of the clinical and radiological records of all patients treated at our center by intracranial stenting in the setting of acute ischemic stroke between January 2010 and December 2020. A systematic review of the literature was conducted according to the PRISMA-P guidelines for relevant publications from January 1976 to December 2020 on intracranial artery dissection treated by stent. RESULTS Seven patients with intracranial artery dissections underwent acute stenting with concomitant tirofiban during the study period. Mid-term follow-up showed parent artery patency in 6/7 cases (85.7%). The modified Rankin Score was 0-2 at 3 months in 5/7 cases (71.4%). The literature review identified 22 patients with intracranial artery dissection treated with acute stenting in association with different antithrombotic therapies. Complete revascularization was obtained in 86.3% of cases with a modified Rankin Score of 0-2 in 68% of patients at 3-month follow-up. CONCLUSIONS Acute intracranial stenting together with intravenous tirofiban administration could be a therapeutic option in patients with intracranial artery dissection and a small ischemic core.

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Background: Intracranial artery dissection is an uncommon cause of acute ischemic stroke. Although acute stenting of the dissected arterial segment is a therapeutic option, the associated antiplatelet regimen remains a matter of debate. *Objectives:* To evaluate the efficacy and safety of acute intracranial stenting together with concomitant intravenous administration of tirofiban and to perform a systematic review of the literature. *Materials and methods:* A single-center, retrospective study of the clinical and radiological records of all patients treated at our center by intracranial stenting in the setting of acute ischemic stroke between January 2010 and December 2020. A systematic review of the literature was conducted according to the PRISMA-P guidelines for relevant publications from January 1976 to December 2020 on intracranial artery dissection treated by stent. *Results:* Seven patients with intracranial artery dissections underwent acute stenting with concomitant tirofiban during the study period. Mid-term follow-up showed parent artery patency in 6/7 cases (85.7%). The modified Rankin Score was ≤ 0-2 at 3 months in 5/7 cases (71.4%). The literature review identified 22 patients with intracranial artery dissection treated with acute stenting in association with different antithrombotic therapies. Complete revascularization was obtained in 86.3% of cases with a modified Rankin Score of ≤ 0-2 in 68% of patients at 3-month follow-up. *Conclusions:* Acute intracranial stenting together with intravenous tirofiban administration could be a therapeutic option in patients with intracranial artery dissection and a small ischemic core.

Key Words: Stroke—Intracranial stent—Tirofiban—Intracranial dissection—Interventional neuroradiology

Nonstandard abbreviations and acronyms: AIS, acute ischemic stroke; IAD, intracranial artery dissection; SR, stent retriever

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Introduction

Intracranial artery dissection (IAD) is an uncommon cause of acute ischemic stroke (AIS) often leading to flow-limiting stenosis.[1–4] Irrespective of whether an IAD is recognized or not, stent retriever (SR) thrombectomy and direct thrombus aspiration are considered as first-line techniques. However, such endovascular treatments could result in a less effective and stable revascularization[5] and stenting of the artery has been reported as an effective treatment for reestablishing the patency of the dissected segment.[1,5–9] Nevertheless, the optimal medical management associated with acute stenting is not well-established. A loading dose of clopidogrel and aspirin is most commonly administered to patients before stent implantation, taking into consideration the time lapse for drug activation. The use of intravenous tirofiban or abiciximab is considered when a prompt antiplatelet effect is required, although their clinical use is off-label for AIS treatment because of the potential increment of bleeding risk.

In this study, we report our experience in treating AIS patients presenting with an IAD by acute stenting performed in association with intravenous administration of tirofiban. We aimed to evaluate the efficacy and the safety of such an approach in the per-operative period and mid-term follow-up. A comprehensive systematic review of the literature was also conducted in order to obtain data regarding the efficacy and safety of intracranial stenting, together with the associated antiplatelet strategy in patients with AIS related to IAD.

Material and methods

Patient population

This is a single-center, retrospective review of the clinical and radiological records of all AIS patients treated at our institution by acute intracranial stenting between January 2010 and December 2020. All patients who received this treatment for a suspected IAD, with the concomitant administration of intravenous tirofiban, were included in the study. The study was approved by the local institutional review board.

Periprocedural digital subtraction angiographies were retrospectively reviewed by two physicians with experience in intracranial stenting (PM, GB) in a consensus reading in order to assess the presence of an IAD as the cause of the AIS, according to specific radiological criteria previously reported by Labeyrie et al.[5] (Table S1). The reviewers also analyzed the immediate follow-up images (CT, MRI) to identify the presence of complications and patency of the stented artery. Finally, patients' clinical records were reviewed to evaluate their mid-term clinical outcome.

Patient selection

According to our institutional protocol, patients presenting with AIS were evaluated by CT scan, CT-perfusion and CT-angiography. Patients referred from peripheral hospitals were directly admitted to the angiography suite. The volume of the ischemic core and penumbra of the former group was calculated using an automated software (RAPID software, iSchemiaView, Redwood City, CA), while the ABC/2 method[10] was used to calculate the ischemic core extent according to diffusion-weighted imaging (DWI) for those referred from peripheral hospitals and selected by MRI. Patients with stroke onset within 8 hours were considered eligible for endovascular treatment, irrespective of the ischemic core extent. For patients admitted more than 8 hours after stroke onset, a cerebral blood flow reduction of $\leq$70mL and a cerebral blood flow/Tmax mismatch ratio of $\geq$1.8 were considered as inclusion criteria for endovascular treatment within 24 hours of symptom onset. Large vessel occlusion in the posterior circulation was considered as eligible for endovascular treatment within 24 hours from symptom onset. Eligible patients received intravenous rt-PA prior to the procedure.

Prediction criteria for IAD

Clinical criteria for a suspicion of IAD were based on patients' young age and the presence of intense headache at the onset of neurological deficits. Radiological criteria for suspecting IAD on the admitting examination (CT/CTA, MRA/MRI) were the focal stenosis or occlusion of the artery, mural hematoma or intimal flap. The following procedural findings were taken into account to establish the diagnosis of IAD at the time of endovascular treatment: obtention of a bypass effect upon stent retrieval, and arterial re-occlusion after stent retriever removal/resheathing.

Endovascular technique

Patients suspected for IAD were treated according to the following algorithm. Endovascular procedures were performed with patients under general anesthesia using a biplane C-arm (Allura Clarity FD20, Philips Healthcare, Best, The Netherlands) via a common femoral artery approach. According to our institutional protocol, the procedures were performed without heparinization. A large-bore aspiration catheter was advanced over a microcatheter (Headway 0.21; MicroVention, Aliso Viejo, California, USA) at the proximal margin of the dissection and negative pressure was applied to perform a direct thrombus aspiration. A stent retriever (SR) (Solitaire FR, Medtronic, Dublin, Ireland; TREVO Striker, Kalamazoo, MI, USA) was unsheathed across the dissection in order to obtain a bypass effect.

If the normalization of the arterial caliber was achieved, the SR was re-sheathed, while the delivery microcatheter was advanced during the re-sheathing beyond the dissected segment, with an intravenous bolus of tirofiban (10 μg/kg) administered over a period of 3 minutes, according to the patient's body weight.[11] Finally, after 5-10

minutes,[11,12] a self-expanding intracranial stent with a complete section (Enterprise, Codman Neurovascular, Raynham, MA, USA) was deployed via the same microcatheter across the dissected arterial segment. When required, due to the extent of the dissection, a second stent (Neuroform Atlas Stryker, Kalamazoo, MI, USA; Solitaire AB) was deployed to completely cover the dissected segment.

Immediately after the intravenous bolus, an intravenous infusion of tirofiban (0.1 μg/kg/min) was maintained for up to 24 hours. After a CT-angiography or MRI performed to confirm stent patency and to exclude intracranial hemorrhage, a loading dose of 300 mg of clopidogrel was administered 6 hours before the end of the tirofiban infusion. Patients were monitored in the intensive care unit during the 24-hour postoperative period. At 48 hours, 75 mg of clopidogrel associated with 100 mg of aspirin were administered to the patients as a long-term therapy (6 months), followed by indefinite therapy with aspirin. Mid-term patency (between 3 and 6 months after the procedure) of the stent was evaluated by CT-angiography, magnetic resonance angiography or transcranial Doppler.

Patient outcome criteria

Clinical and radiological outcomes of patients were assessed according to the following criteria: patency of the stented artery, together with the occurrence of ICH at the immediate and mid-term follow-up (3-6 months); shift of the NIHSS at 24 hours after the procedure; and clinical outcome at day 90 according to the modified Rankin Score (mRS) scale.

Literature review

Data sources and searches

Three online databases (Embase, PubMed and the Cochrane library) were searched for articles published between January 1976 and December 2020 on IAD treated by stent according to the PRISMA-P guidelines (Table S2). Medical subject headings and keyword searches included the terms ((stroke) AND (intracranial artery dissection)) NOT (aneurysm). In addition, the reference lists of selected articles and pertinent available non-systematic analyses were reviewed for other potential citations. Data from unpublished sources were not searched or included.

Study selection and data extraction

Two investigators (GB and PM) conducted independent literature searches and data extraction using a standardized approach. Based on title and abstract screening, selected publications were initially reviewed by the same investigators to assess if the studies met the inclusion criteria, i.e. studies describing patients with AIS due to an IAD treated by intracranial stenting in the acute phase. Exclusion criteria were studies concerning extracranial isolated dissection, conservative management without endovascular treatment, case reports and non−English language publications, congress abstracts, letters to the editor, and atherosclerotic intracranial stenosis. Studies describing extracranial arterial dissection, medical or diagnostic management of an IAD were also excluded after full text assessment. Any disagreement was resolved by a third author (Fig. 1). The following data were extracted: number of patients; patient characteristics; intervention characteristics; complications; symptomatic intracranial hemorrhages; functional outcomes; and mortality. Bias risk assessment was assessed by the Cochrane Collaboration's Risk of Bias Tool.[13]

Study outcomes

IAD reperfusion after stenting was evaluated overall in the included studies and the clinical outcome was graded according to the mRS at 3 months, with a mRS ≤ 2 considered as a favorable outcome.

Statistical analysis

Descriptive statistics were performed. Patient characteristics and discrete variables were presented as mean +/- standard deviation (SD). Continuous variables were presented as mean +/- SD or as the median, 25th and 75th percentile.

Results

Case series

A total of 64 patients presenting with an AIS due to large-vessel occlusion were treated at our center by intracranial stenting during the study period. Among these, we identified 7 patients with AIS related to an IAD treated by acute stenting and concomitant administration of tirofiban. Moreover, thirteen additional patients presenting with an intracranial dissection associated with an intracranial hemorrhage were admitted at our center during the study period. Given the different clinical and therapeutic implications of such condition, this group of patients was not considered for the aim of the present study.

Patient characteristics are shown in Table 1 (mean age 37.4 [standard deviation (SD) 13.2]; 4 [57.1%] were female).

Mean ischemic core volume was 6.75 ml (range 0-31 ml) in 6 patients and the mean onset to groin was 219 minutes (SD 106 minutes). Dissected arteries were the M1 segment of the middle cerebral artery (n=2/7), supraclinoid segment of the internal carotid artery (n=3/7), internal carotid terminus (n=1/7), and V3 segment of the vertebral artery, extending to the proximal and middle-third of the basilar artery (n=1/7). In 5/7 cases (71.4%), intravenous rt-PA was administered.

The direct thrombus aspiration used as the first-line approach (n=5/7) was ineffective in establishing recanalization in all cases. A SR was subsequently deployed

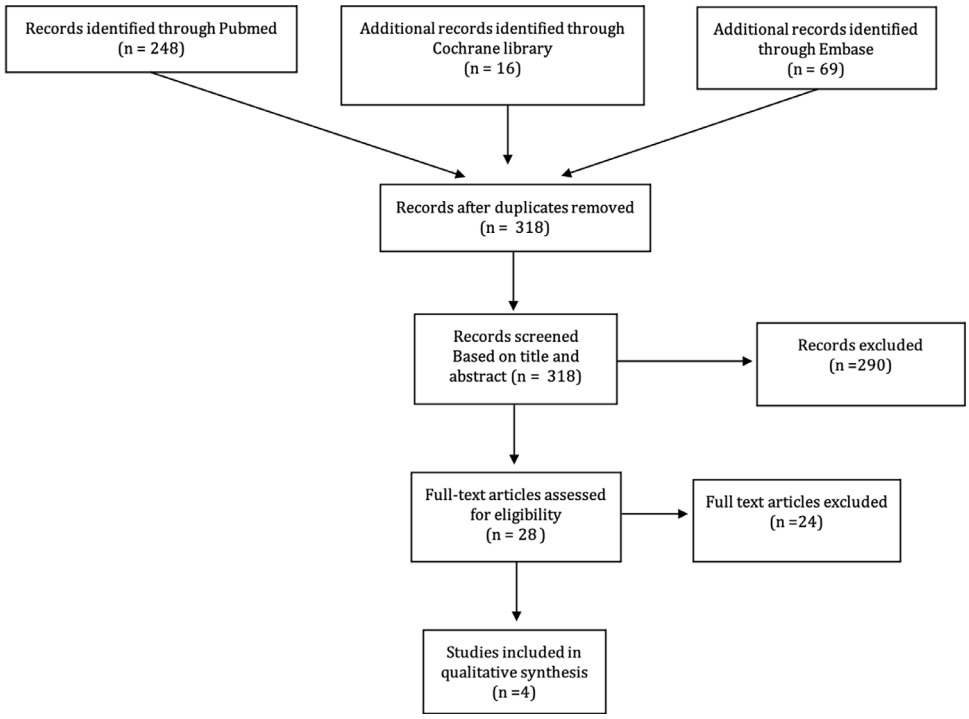

Fig. 1. *PRISMA-P flow diagram.*

within the dissected portion of the artery in order to verify if the artery regained a normal lumen upon stent deployment. In each case, the "bypass effect" achieved by the SR confirmed the suspicion of an IAD. Consequently, the SR was re-sheathed into a delivery microcatheter without any SR thrombectomy attempt in 5/7 cases. The delivery microcatheter was advanced during the re-sheathing beyond the dissected segment and used to implant a stent covering the complete IAD section (Fig. 2).

An Enterprise stent was used as a permanent stent in all cases (n=7/7). In 2 cases, a second stent was added (Solitaire AB [n=1/7]; Neuroform Atlas [n=1/7]). An intravenous bolus of tirofiban (10 μg/kg) was administered to all patients in a 3-minute time lapse according to body

Table 1. *Patients' baseline characteristics, per-operative data and clinical evolution.*

	PT. 1	PT.2	PT.3	PT.4	PT.5	PT.6	PT.7
Gender	F	M	M	F	F	F	M
Age (years)	30-39	10-19	30-39	50-59	30-39	20-29	50-59
IAD location	M1 left	ICA left	M1 right	V-B	ICA left	ICA right	ICA T left
Mural hematoma	yes	yes	yes	yes	yes	yes	yes
Arterial stenosis/occlusion	yes	yes	yes	yes	yes	yes	yes
Intimal flap	yes	yes	yes	yes	yes	yes	no
Artery normalization	yes	yes	yes	yes	yes	yes	yes
Ischemic core	3 ml	1 ml	0 ml	-	31 ml	5.5 ml	0
Ischemic penumbra	102 ml	-	126 ml	-	109 ml	117ml	62 ml
rtPA i.v.	yes	yes	no	no	yes	yes	yes
Onset to groin	135 min.	245 min.	235 min.	380 min.	320 min.	110 min.	110 min.
Tirofiban	yes	yes	yes	yes	yes	yes	yes
Stent patency	yes	yes	yes	yes	yes	yes	no
NIHSS admission	18	17	8	15	15	15	4
NIHSS discharge	2	2	4	2	4	0	24
Hemorrhagic complications	no	no	no	no	no	no	no
Mid-term stroke recurrence	no	no	no	no	no	no	no
mRS at 3 months	2	0	1	2	3	1	5
Stent patency at follow-up	yes	yes	yes	yes	yes	yes	no

IAD, intracranial artery dissection; i.v., intravenous; V-B, vertebra-basilar; T, terminus.

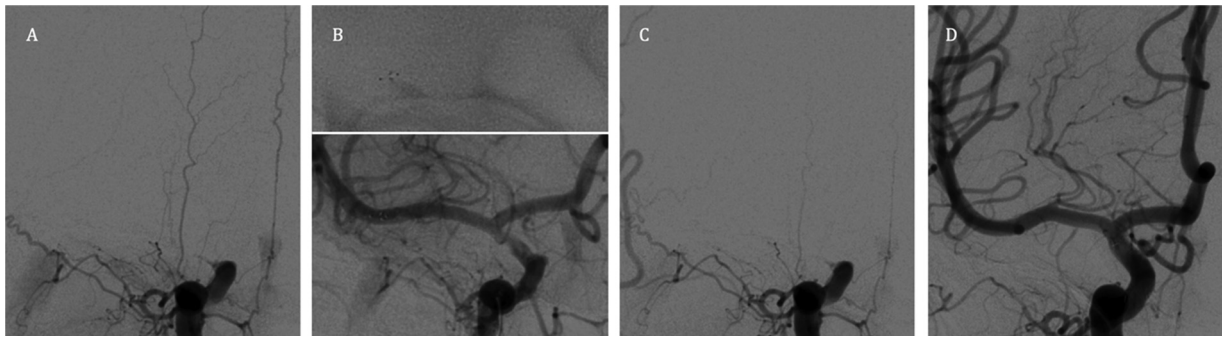

Fig. 2. *Dissection of the supraclinoid segment of the right internal carotid artery. A) initial occlusion; B) image performed with unsheathed stent retriever; C) result after stent retrieval; D) result after final stent implantation and intravenous bolus of tirofiban.*

weight and the stent was deployed 5-10 minutes after this bolus.[11,12] An intravenous infusion (0.1μg/kg/min) of tirofiban was also administered at the same time and maintained for up to 24 hours. In 6/7 cases, the stent was patent after delivery. In the remaining case, the stent occluded a few minutes after the initial post-deployment control had showed patency of the device. This patient developed a large ischemic lesion of the related brain parenchyma and had a poor clinical outcome at the mid-term follow-up. There were no cases of hemorrhagic complications.

In 6/7 cases, the neurological evaluation at 24 hours from onset showed an important clinical improvement associated with a substantial decrease of the NIHSS at discharge (mean 5.43 points [SD 8.30]) compared to the admission NIHSS (mean 13.14 points [SD 5.14]) (Table 1). No patients had ischemic stroke recurrence in the follow-up period. The mRS at 3-months' follow-up was 0-2 in 5/7 patients (71.4%), while one patient presented a mRS 3, and one a mRS 5. At mid-term follow-up, 6/7 involved arteries were patent and without residual intra-stent stenosis.

Literature review

Search results

The initial database search yielded 333 articles. After removal of duplicates, 318 studies remained. Thirty-one non-English language articles were then removed and the remaining studies were screened by analyzing the title and abstract. Twenty-eight full text articles were assessed for eligibility. At the end of the process, four studies with a total of 22 patients were included in the qualitative synthesis. The results of our literature screening are summarized in Table 2.

All included publications were retrospective case series. Hence, an overall high risk of bias was associated with the included studies (Table S3). Only two domains presented a low risk of bias, namely, outcome measurements and selection of the reported results (Table S3).

Procedural data and IAD treatment

In the included studies, all IAD were managed by endovascular treatment, i.e. intracranial stenting. Two series used tirofiban as an antithrombotic drug,[8,14] while a combination of aspirin and clopidogrel was used in 3/4 studies.[5,7,14] In one series, abiciximab was also used.[5]

Reperfusion data and clinical outcome

Reperfusion data were reported in all studies. A complete reperfusion was achieved in 19/22 patients (86.3%). Clinical outcome was generally assessed using the mRS at 3 months. In 15/22 patients (68%), mRS was ≤ 2 at follow-up.

Discussion

Our systematic literature review showed that intracranial stenting in patients with AIS due to an IAD (Table 2) could be considered a valuable therapeutic option for selected patients. In particular, a complete recanalization was achieved in in 86.3% of cases, resulting in a good clinical outcome (mRS ≤2) in 68% of cases at 3 months' follow-up. The results of our clinical study are in line with those of the systematic literature review with respect to the efficacy and safety of acute intracranial stenting and also suggest a potential use for a concomitant intravenous administration of tirofiban for IAD treatment. In our series, such management was effective in 6/7 cases (85.7%) and a complete artery revascularization was achieved without significant residual intra-stent stenosis at midterm follow-up, with a 3-months' mRS ≤ 2 in 5/7 patients (71.4%). Conservative management with rt-PA and/or antiplatelets or anticoagulants has been described as an effective treatment for IAD, especially in the case of mild neurological deficits.[15,16] Although endovascular treatment can be considered for selected patients with large vessel occlusions, being stent reconstruction is a reasonable option.[16]

IADs that present with ischemic symptoms have a lower risk of intracerebral hemorrhage compared to those with subarachnoid hemorrhage.[5,17] However, as widely

Table 2. *Studies included in the literature review.*

Study	N patients	Onset to reperfusion median	Thrombectomy	Stent	Tirofiban	Abciximab	Aspirine + clopidogrel.	Reperfusion	sICH	ISS	mRS 0-2 3m
Jeon et al. 2010	3	-	no	3/3	3/3	0	0	3/3	0	0	3/3
Kim et al. 2015	22	20 h (IQR 14.1-89.2)	no	8/22	0	0	8	8/8	0	0	8/8
Labeyrie et al. 2018	13	-	yes	7/13	0	yes	yes	7/7	0	2/7	4/7
Forbrig et al. 2019	4	4 h (IQR 3.8-5.7)	yes	4/4	3/4	0	1/4	1/4	2/4	1/4	0/4

ISS, in-stent stenosis; sICH, symptomatic intracranial hemorrhage; IQR, interquartile range.

reported, any anti-thrombotic therapy administered to patients with AIS increases the risk of intracerebral hemorrhage.[18–20] The efficacy and safety of tirofiban has already been evaluated for intracranial aneurysms,[21–24] as well as for AIS.[14,25–27] Nevertheless, in patients with AIS, the size of the ischemic core and the time of onset have to be considered before any administration of antiplatelet therapy to assess the risk of hemorrhage. To our knowledge, the present study represents the largest series of IAD treated by acute stenting and intravenous tirofiban. Importantly, there were no cases of hemorrhagic complications.

In the studies included in our systematic literature review, aspirin and clopidogrel were used as antithrombotic therapy for intracranial stent implantation in 3/4 studies. Tirofiban was administered in 6/22 cases, but resulted in a good clinical outcome in only 50% of patients. Forbrig et al.[14] treated IADs with acute stenting and used tirofiban in 3/4 cases as rescue treatment after SR thrombectomy. They obtained a low reperfusion rate after stent implantation, with relatively poor patient outcomes as no patient had an mRS $\leq$2 at 3 months and 2/4 patients suffered a symptomatic intracerebral hemorrhage.[14] By contrast, Jeon et al.[8] performed intracranial stenting together with tirofiban as first-line treatment for IAD in three cases without any attempt of SR thrombectomy and reported obtaining a complete reperfusion associated with good clinical outcome (mRS $\leq$2 at 3 months) in most cases, without any symptomatic intracerebral hemorrhage.

Therefore, it could be argued that the differences in terms of procedure success and outcome of the two studies were related to the absence of thrombectomy maneuvers in the study in which artery stenting was considered as first-line treatment, given that STR passes are potentially associated with the further dissection and damage of the target vessel. IAD is frequently under-recognized during the acute phase of ischemic stroke[3] and intracranial stenting is frequently considered as a rescue technique[5,14,25,26,28] for patients in whom first-line thrombectomy strategies do not result in a stable revascularization. In our opinion, early identification of an IAD is crucial for the success of the stenting procedure.

SR thrombectomy may lead to endothelial damage[29] that may interfere with stent deployment in the case of stroke-related IADs, regardless of the antiplatelet regimen. In our series, an IAD was suspected before the procedure in all patients according to the patient's associated risk factors and radiological criteria, such as the admitting CT/CT-angiography or MRI/MRI-angiography, together with initial DSA imaging, according to the criteria already mentioned previously. No SR thrombectomy was performed before stent deployment and tirofiban administration in 5/7 cases, allowing to obtain a complete revascularization in 6/7 cases. All patients presented a small ischemic core at admission and no symptomatic

hemorrhagic complication occurred despite the association between rt-PA and tirofiban, also in the case of stent occlusion that leads to a large infarct volume.

Only small clinical series or case reports have described the efficacy of acute stenting for IAD.[1,5–9,14] Labeyrie et al.[5] reported 13 cases of IAD treated with medical therapy, mechanical thrombectomy or acute stenting. In their study, stenting of the target artery was performed in 7/13 cases and was significantly associated with a lower rate of residual dissection-related stenosis compared with SR thrombectomy or medical therapy. Moreover, IADs treated with stent deployment had a lower ischemic recurrence compared with the other treatments. In another study, Kim et al.[7] reported eight IADs treated with stenting, achieving a 3-month mRS of 0-2 in all patients. In this study, all stents were patent without significant residual intra-stent stenosis at angiographic follow-up. In both of the above-mentioned studies,[5,7] most patients had longer onset-to-groin-times compared to our study population as they had neurological symptoms at admission related to crescendo strokes, and most received premedication with a loading-dose of dual antiplatelet drugs before stent implantation. In our study, all patients presented with severe neurological deficits at admission. Consequently, the onset-to-groin-times was short compared to previous studies. An intravenous bolus of tirofiban was administered to all patients 5 to 10 minutes before stent implantation, followed by a maintenance infusion over the next 24 hours. This treatment protocol was established to secure a rapid and effective antiplatelet therapy prior to stent implantation, knowing that the complete antithrombotic effect of clopidogrel (loading dose of 600 mg) is achieved only between 2 and 4 hours after its administration.[30]

As previously reported by Woo et al.[26] the intravenous administration of tirofiban concomitant with stent deployment was related to a significantly lower rate of acute in-stent thrombosis, as well as a better clinical outcome compared to patients who did not receive tirofiban. This finding was confirmed by our experience. In 6/7 cases, the stents were patent at mid-term follow-up and without signs of intra-stent stenosis. In addition, none of these 6 patients presented a recurrence of ischemic stroke during the follow-up period. A novel alternative pharmacological option that is gaining consensus among neurointerventionalists is the use of intravenous P2Y12 receptor antagonists both for patients with AIS and those with hemorrhagic stroke who need prompt antiplatelet therapy.[31–34] Nevertheless, reports and evidence for such drug use in cases of IAD are lacking.

Study limitations

Our study has several limitations related to its retrospective design, single-center setting and the small number of patients. In addition, tirofiban is not available in all countries, thus limiting the generalization of the results. However, it should be noted that the rarity of IAD published reports has so far precluded a definition of a standard of care for such a disease and further research is needed.

Conclusions

Our study suggests that intracranial stenting of IAD with concomitant tirofiban administration in the acute phase is an effective and safe endovascular treatment in patients with a small ischemic core.

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Competing interests

PM is consultant for Medtronic and Stryker. All other authors declare no competing interests.

Contributors

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work; revising it critically for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

Data sharing statement

All the data are available upon request to the corresponding author.

Patient consent for publication

Not required.

Ethics approval

Ethics approval was obtained from the local institutional review board.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2021.105891.

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